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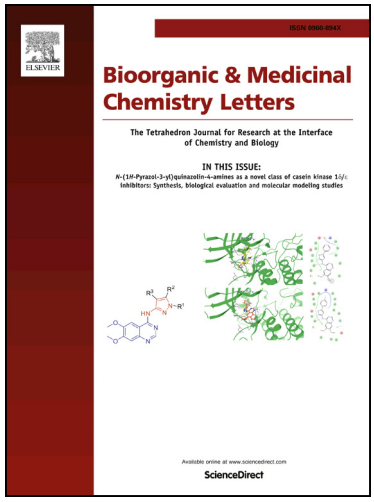

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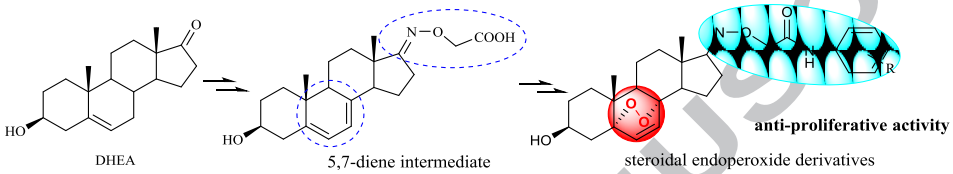

DHEA — 5,7-diene intermediate — steroidal endoperoxide derivatives

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ABSTRACT

Inspired by the significant anti-cancer activity of our previously screened natural ergosterol peroxide (EP, **1**), we synthesized and characterized a series of novel 5α,8α-epidioxyandrost-3β-ol-17-(*O*-phenylacetamide)oxime derivatives (**9a-o**). The anti-proliferative activity of the synthesized compounds against human hepatocellular carcinoma cells (HepG2, SK-hep1) and human breast cancer cells (MCF-7, MDA-MB231) were investigated. Compounds **9d**, **9f**, **9h**, **9j** and **9m** displayed good anti-proliferative activity (most IC_{50} < 20 μM) in vitro. Furthermore, fluorescence imaging showed that the designed coumarin-**9d** conjugate (**12**) localized mainly in mitochondria, leading to enhanced anticancer activities over the parent structure.

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Nowadays, natural drugs have attracted extensive attention in health promotion and disease treatment including cancer.[1] In addition, natural product-based drug discovery is a major route leading to developing therapeutic drugs for various diseases.[2] Natural endoperoxides (EPOs) are cyclic organic compounds, with an O-O single bond as a peroxide bridge.[3] EPOs include 1,2-dioxanes, 1,2,4-trioxanes and 1,2,4,5-tetraoxanes, all of which possess the critical peroxide linkage.[4] They are important pharmacophores in a number of natural biologically active compounds. Although best known as potent antimalarials,[5] a number of natural EPOs also exhibit a range of activities which encompasses antifungal, antiviral and anticancer activity (Fig.1).[6-9]

Steroidal compounds have drawn attention not only due to unusual and interesting chemical structures, but also due to their widespread application as anti-inflammatory, diuretic, anabolic, contraceptive, and anticancer agents.[10,11] Most steroidal drugs in use today are semi-synthetic compounds and widely used in traditional medicines by the modification of the steroid ring system and side chains.[12,13] The interesting structural and stereochemical features of the steroid nucleus provide additional fascination to the researchers, and thereby the introduction of heteroatom, heterocycle, amides or replacement of one or more carbon atoms in the steroidal skeleton has been envisaged to discover new chemical entities with a potential to afford some promising drugs of the future and brings notable modifications of its biological activity.[14,15]

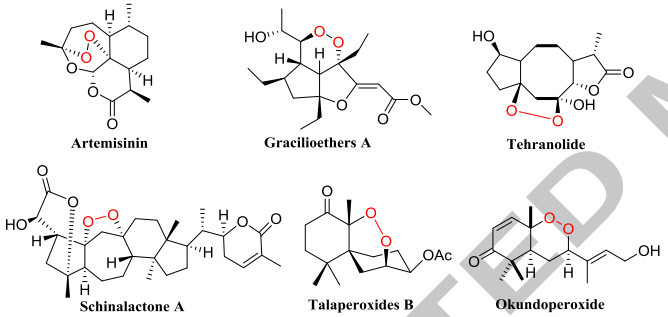


Fig. 1. Structures of natural endoperoxides with bioactivities.

Among natural EPOs, steroidal 5α,8α-endoperoxides are the important active lead compounds in drug discovery.[16] Ergosterol peroxide (5α,8α-epidioxiergosta-6, 22-dien-3β-ol, EP, **1**) (Fig. 2), is a member of a class of fungal secondary metabolites of sterol 5α,8α-endoperoxide derivatives. It can be isolated from many medicinal fungi, such as *Sarcodon aspratus*, *Hericium erinaceum*, *Armillariella mellea*, *lactarius hatsudake*, *hypsizigus marmoreus*.[17-19] It has been reported that **1** can inhibit tumor growth by anti-angiogenesis or cytotoxicity.[20] In our previous study, we found that **1** purified from *Ganoderma lucidum*, induced human cancer cell death.[21,22]

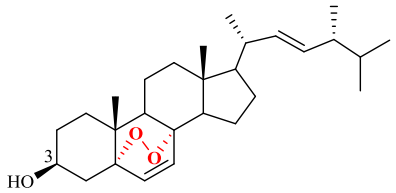


Fig. 2. The structure of ergosterol peroxide (EP, **1**)

As an important active lead compound in drug discovery, **1** is well known for its 5α,8α-peroxy moiety. In this context, we have recently developed a simple and practical synthetic route to obtain novel series of sterol 5α,8α-endoperoxides from readily available dehydroepiandrosterone (DHEA, **2**) (Fig. 3). The synthesis of endoperoxides achieved by the reaction of sterol 5,7-dienes intermediate with singlet oxygen ($^1O_2$)[23]. It is also noticeable that oximes are important chemical compounds, possessing versatile chemical applications and have been used as protecting group,[24] as intermediates for the synthesis of amides,[25] nitro,[26] amines[27] and aza heterocycles.[28] In our previous studies, we synthesized several classes of sterol 5α,8α-endoperoxides and found that some derivatives displayed distinct cytotoxic activity against some cancer cells.[29-31] In the present study, we decided to keep the steroidal skeleton and the 5,8-peroxy moiety, and pay our attention to the side chain of **1**. Hence, the different amide derivatives were synthesized by introduction of 17-(*O*-carboxymethyl)oxime coupled aromatic group into the linear compound **1** for the first time (Fig.3).

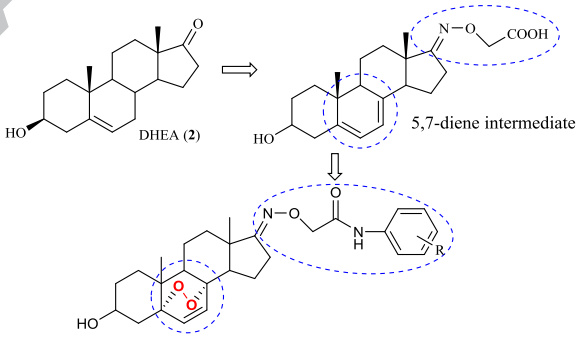
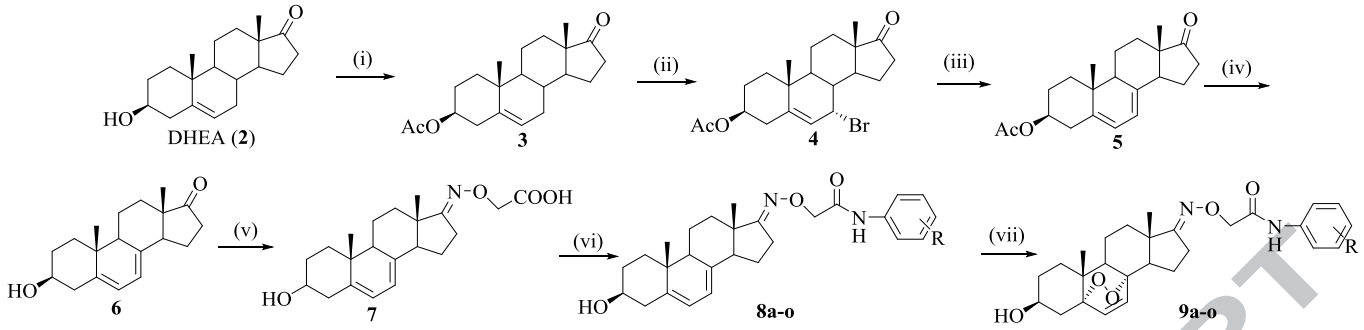


Fig. 3. Molecular structures of DHEA, sterol 5,7-dienes intermediate and designed strategy of target compounds.

Using natural and commercially available DHEA (**2**) as the starting material, all designed derivatives were synthesized via the routes outlined in Scheme 1. Compound **3** was prepared via acetylation of **2**, which then bromized by NBS (**4**) and debrominated by Bu_4NF to afford 5,7-diene acetate **5**.[32] Subsequently, compound **6** was obtained after deacetylation reaction of **5** in 30% overall yield from **2**. Then, treatment of **6** with carboxymeth-oxylamine hemihydrochloride in ethanol delivered the 17-(*O*-carboxymethyl) oxime intermediate **7**.[33] The side chains of **8a-o** with the desired configuration at C-21 were introduced by acylation reaction of carboxylic acid **7** with different anilines. The details of the synthesized compounds **8a-o** were given in Table 1.



Scheme 1. Synthesis of EP derivatives **9a-o**. (Reagents and conditions: (i) Ac_2O, DCM, Pyridine, RT; (ii) NBS, cyclohexane, reflux, 1 h; (iii) Bu_4NF, THF, RT, 12 h; (iv) NaOMe, MeOH, RT, 12 h; (v) $NH_2OCH_2COOH{\cdot}HCl$, EtOH, KOH, reflux, 3 h, HCl; (vi) anilines, DMF, HATU, DIPEA, RT, 8 h; (vii) O_2, Photosensitizer, pyridine, *hv*, 0 °C, 0.5 h.)

Table 1. Synthesis of intermediates **8a-o**

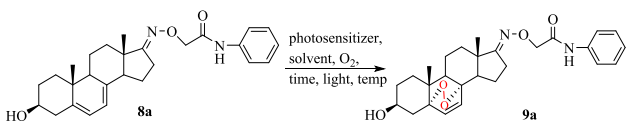
Entry	Compounds	-Ar-R	Yield[a]
1	**8a**	C_6H_5	92
2	**8b**	4-Me-C_6H_4	87
3	**8c**	3-Me-C_6H_4	85
4	**8d**	4-*i*-Pr-C_6H_4	77
5	**8e**	3-Ethynyl-C_6H_4	75
6	**8f**	3-Cl-4-Me-C_6H_3	86
7	**8g**	4-Br-C_6H_4	83
8	**8h**	4-Cl-C_6H_4	88
9	**8i**	3-Cl-C_6H_4	86
10	**8j**	3-Cl-4-F-C_6H_3	92
11	**8k**	4-F-C_6H_4	89
12	**8l**	3-F-C_6H_4	90
13	**8m**	3-CF_3-C_6H_4	88
14	**8n**	4-OMe-C_6H_4	84
15	**8o**	3-OMe-C_6H_4	85

[a] Isolated yields

The photooxygenation reaction of **8a-o** is the key step of the whole synthetic route and its reaction conditions had to be optimized in order to get high conversion. A typical experimental procedure for the optimization of the photooxygenation reaction conditions was described using **8a** as an example (Table 2). Finally, photooxidation of **8a-o** with eosin Y as photosensitizer in pyridine, irradiated with iodine tungsten lamp and kept bubbling oxygen for 0.5 h to get target compounds **9a-o**. Other conditions such as reaction temperature and light source were chosen based on the results shown in Table 2 (entry 3).

Crystal of **9a** suitable for single-crystal X-ray diffraction was obtained by slow crystallization from *n*-hexane/ethyl acetate solution at ambient temperature. X-ray crystal structure of **9a** was obtained and presented in Fig. 4. The structure confirms the α-stereochemistry of the peroxy bond at C-5 and C-8 positions, and oxime-phenylacetamide side chain at C-17 position. Crystallographic data for **9a** have been deposited at the Cambridge Crystallographic Data Center with CCDC numbers 1450591.

Table 2. Optimization of the photooxygenation reaction conditions.



Entry	Photosensitizer[a]-Solvent[b]	Light[c]	Time (h)	Yield[d] (%)
1	EY-Py	100 W	0.5	12
2	EY-Py	300 W	0.5	36
3	EY-Py	500 W	0.5	62
4	EY-Py	500 W	1.0	67
5	MB-Py	300 W	0.5	22
6	MB-Py	500 W	0.5	34
7	MB-Py	500 W	1.0	46
8	EY-EtOH	300 W	0.5	15
9	EY-EtOH	500 W	0.5	26
10	MB-EtOH	500 W	0.5	17

[a] Photosensitizer: EY (eosin Y); MB (methylene blue); [b] Solvent: Py (pyridine); EtOH (anhydrous ethanol). [c] Light: Iodine-tungsten lamp 220 V (100, 300, 500 W). [d] Isolation yield. Others: O_2 (high purity oxygen, > 99.995%); Temperature: Ice-water bath.

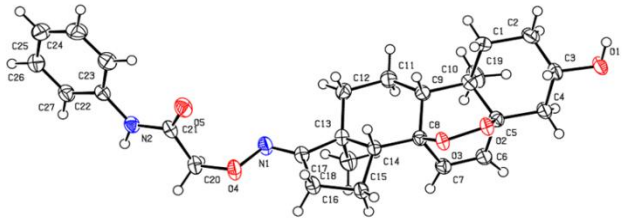


Fig. 4. X-ray crystal structure of **9a**.

The newly synthesized endoperoxides **9a-o**, some **8a-p** and **1** were evaluated for their anti-proliferative activities against human cancer cell lines derived from various human cancer types, including human hepatocellular carcinoma cell lines (HepG2, Sk-Hep1) and human breast cervical cancer cell lines (MDA-MB231, MCF-7). *In vitro* cell-based evaluation of the anti-proliferative activities of the synthesized compounds was carried out using MTT assay. Cisplatin was employed as the positive control. The anticancer potency of these compounds were indicated by IC_{50} values. The results were summarized in Table 3.

Compounds **9d**, **9f**, **9h**, **9j** and **9m** were the most promising compounds amongst the tested derivatives. Regarding the structure activity relationship, a number of correlations can be made from this data based on steric and electronic properties of the compounds. Most of the endoperoxides, including **1** and **9a-p** which have peroxidic bridge at the B-ring of the sterol skeleton exhibited potent activity against all the tested cell lines. Compounds **8a** and **8o**, which have no peroxidic bridge at the C-5 and C-8 positions exhibited barely inhibition activity against all the tested cell lines (IC_{50} > 40 μM). Preliminary SAR studies showed that the peroxidic bridge at the C-5 and C-8 positions is requisite pharmacophore for inhibition activity.

Besides, it is also interesting to note that the type of aryl substituent on side chain provide opportunity to further amplify the cytotoxic activity. Compound **9f** with 3-Cl-4-Me-C_6H_3 substituent on side chain has shown highest growth inhibition

activity (Table 3, entry 6) particularly against the four cancer cell lines as compared to other endoperoxides. Compound **9d** with 4-*i*-Pr-C_6H_4, **9j** with 3-Cl-4-F-C_6H_3, and **9m** with 3-CF_3-C_6H_4 substituents are next to the compound **9f** have shown relatively better activity. The electronic effect by fluoro or chloro substituent on cytotoxicity has already been reported.[34,35] On the other hand, compounds **9a**, **9b** and **9c** with simple phenyl/tolyl substituent (*i.e.* without heteroatom substituent) on side chain have shown barely inhibition activity against all the cell lines. Probably the electron withdrawing nature of these heteroatom substituents present on above endoperoxides also contributes additional control on cell growth inhibition. Furthermore, among the five promising compounds, compound **9d** possesses isopropyl group substituent in the side chain was next to the compound **9f** have shown relatively better activity. The probably SAR for this compound was that isopropyl group at the terminal of side-chain, which was easier to get through the membrane.

What's more, compounds **8f** and **8m** without peroxide bridge showed relatively better inhibition activity, which means the side chains and peroxide bond would provide synergistic effect for the bioactivity. On the whole, it appeared that substituent changes to the C-17 position could serve as a promising launch point for further design of this type of steroidal anticancer agents.

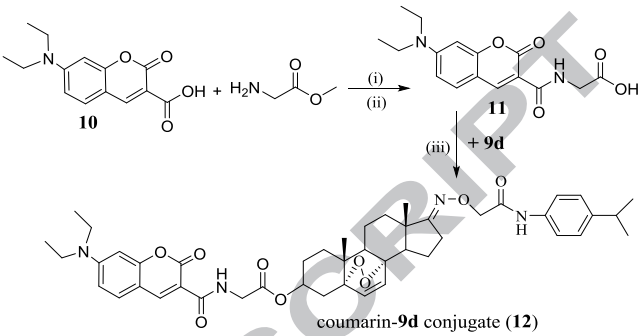
Table 3. *In vitro* anti-proliferative activities of compounds.

	IC_{50} (μM)[a]			
Compd	HepG2	Sk-Hep1	MCF-7	MDA-MB231
9a	48.33	60.42	>80.00	74.24
9b	38.34	46.33	62.24	>80.00
9c	35.42	30.57	41.60	45.53
9d	12.14	14.63	20.36	15.82
9e	44.18	38.25	31.62	25.07
9f	9.30	12.12	22.74	17.53
9g	29.89	24.40	40.32	37.46
9h	14.84	11.08	19.50	14.25
9i	15.42	22.82	34.35	29.52
9j	11.34	14.26	26.22	24.58
9k	15.78	10.66	14.50	12.74
9l	40.54	37.62	29.47	26.30
9m	13.50	15.63	23.06	20.35
9n	49.52	41.40	52.24	46.43
9o	44.94	50.22	43.20	57.27
8a	>80.00	73.84	>80.00	>80.00
8d	26.72	23.15	31.59	35.02
8f	17.76	19.82	34.26	29.18
8i	22.74	26.60	42.10	33.52
8m	14.42	16.54	21.30	19.35
8o	70.57	>80.00	>80.00	59.33
1	15.80	17.25	23.34	19.17
Cisplatin	0.45	2.39	6.63	5.50

[a] Data represent the mean values of three independent determinations.

Mitochondria-targeting theranostic probes that enable the simultaneously reporting of and triggering of mitochondrial dysfunctions in cancer cells are highly attractive for cancer diagnosis and therapy.[36-40] Herein, we designed one fluorescent mitochondria-targeting theranostic probe coumarin-**9d** (**12**) through the conjugation of **9d** with a coumarin-3-carboxamide fluorophore.[41] The designed conjugate probe was synthesized via the routes outlined in Scheme 2. We postulated that the fluorescent coumarin-endoperoxide conjugate as mitochondria targeting theranostic probe could efficiently leading to enhance anticancer activities.[42]

With the probe **12** in hand, we first investigated its optical properties (Fig. 5). In general, it possess typical optical properties of the courmarin-3-carboxamide fluorophore,[43] with a maximum excitation wavelength (λ_{ex}) of ~478 nm and emission wavelength (λ_{em}) of ~421.5 nm. The large Stokes shift of probe 56.5 nm ensured good photophysical properties for fluorescence imaging studies in living cells.



Scheme 2. Synthesis of the probe coumarin-**9d** conjugate (**12**). (Reagents and conditions: (i) methyl 2-aminoacetate, HATU, DIPEA, DCM, 2 h, RT, N_2; (ii) 2 M HCl, 1,4-dioxane, 10 h, RT; (iii) DCC, DMAP, DCM, RT, 36 h.)

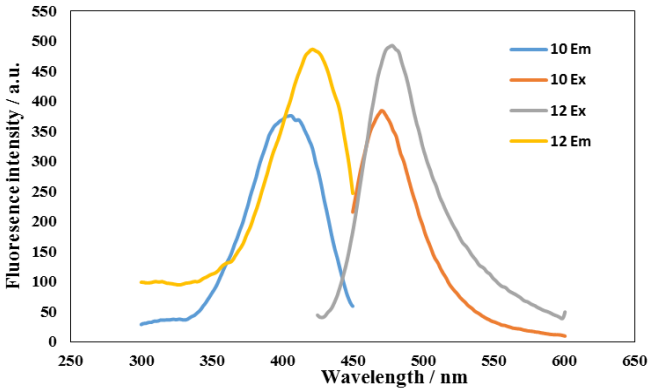


Fig.5. Fluorescence excitation and emission spectra for probes **10** and **12** (1.0 μM in DMSO).

We next examined the subcellular localization of the designed conjugate **12** in living human liver cancer HepG2 cells with the commercially available mitochondria-specific green dye Rhodamine 123 (Rh123; λ_{ex} = 488 nm and λ_{em} = 515-530 nm). Intracellular fluoroscope imaging was explored on a Zeiss 710M confocal laser scanning microscopy (Carl Zeiss, Germany). As shown in Fig. 6b, cells were extensively stained by **12** (10 μM) after 2 h of incubation, and strong blue fluorescence was detected inside the cells with excitation at λ = 430-500 nm, which indicated good cell membrane permeability and high cellular uptake of **12**. The subcellular localization study showed that compound **12** could co-localize strongly with Rh123 in mitochondria, with an extensive blue-green color in the merged fluorescence images of **12** and Rh123 (Fig. 6d).

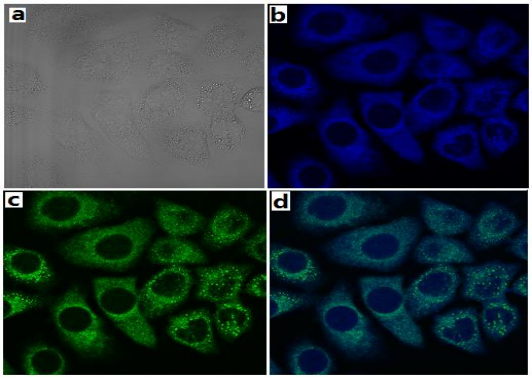


Fig.6. Confocal laser scanning microscopic images of HepG2 cells treated with **12** (10 μM, 2 h) in the presence of Rh123 (0.5 μM, 20 min) in PBS. a) Cell images in bright field. b) Fluorescence images of cells stained with **12**. c) Fluorescence images of cells stained with Rh123. d) Merged images of a and b.

Having proven mitochondrial localization of our designed conjugate, **12**, we then measured the anti-proliferative activities of **12** against four selected human cancer cell lines (HepG2, Sk-Hep1 MCF-7 and MDA-MB231). The results, shown in Table 4, shown that they are cytotoxic to these four cancer cell lines (IC_{50} < 10 μM). We therefore postulated that, upon cell uptake, coumarin fluorophore-mediated delivery of **9d** to mitochondria contributed greatly to enhanced anti-proliferative activity.

Table 4. *In vitro* anti-proliferative activities of compounds **10** and **12**.

	IC_{50} (μM)[a]			
Compd	HepG2	Sk-Hep1	MCF-7	MDA-MB231
10	>100	>100	>100	>100
12	8.40	7.52	9.64	7.22

[a] Data represent the mean values of three independent determinations.

In summary, a series of sterol 5α,8α-endoperoxide derivatives were synthesized and evaluated for their anticancer activities. Some of the synthesized compounds exhibited good anticancer activities against the four tested cancer cell lines *in vitro*. In particular, compound **9d**, **9f**, **9h**, **9j** and **9m** were the most promising derivatives, with IC_{50} values ranging from 9.3-20 μM, against all the four cancer cell lines respectively. Substituent changes to the C-17 position can affect potency against different kinds of cancer cell lines. Fluorescence images showed that the designed coumarin-**9d** (**12**) conjugate localized mainly in mitochondria, leading to enhanced anticancer activities over **9d**. Future work will focus on the synthesis of additional candidate structures with different side chains to address specific cancer cell lines. It appeared that substituent changes to the C-17 position could serve as a promising launch point for further design of this type of steroidal anticancer agents.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at